Expanding NEURON extracellular reaction-diffusion support: simulation of ischemic stroke

Adam JH Newton[1,2], Alexandra H Seidenstein[2,5], Robert A McDougal[1,3], Michael Hines[1], William W Lytton[2,4,6]

1. Department of Neuroscience, Yale School of Medicine, New Haven, USA.
2. Department of Physiology and Pharmacology, State University of New York Downstate Medical Center, Brooklyn, USA.
3. Center for Medical Informatics, Yale University, New Haven CT 06510, USA
4. Department of Neurology, State University of New York Downstate Medical Center, Brooklyn, USA.
5. NYU School of Engineering, 6 MetroTech Center, Brooklyn, NY 11201, USA
6. Department of Neurology, Kings County Hospital Center, Brooklyn, NY 11203, USA.

The NEURON simulation platform, featured in over 1900 publications, traditionally focused on models of neurons and networks of neurons. NEURON's reaction-diffusion module (*rxd*) expanded support for 1D and 3D intracellular reaction-diffusion models. These have been used to probe intracellular calcium dynamics in dystonia, impedance mismatch and persistent neuronal activity via HCN channels.

Originally *rxd* provided only limited extracellular support with isolated compartments around each segment. Recently *rxd* has been extended to include coarse-grained macroscopic models of the extracellular space. NEURON thus allows detailed cell models to be embedded in a 3D macroscopic model of tissue. Extracellular diffusion is implemented using the Douglas-Gunn alternating direction implicit method, an efficient scheme which supports parallelization. Reactions are now implemented using Just-In-Time compilation, allowing numerical integration to use faster compiled code rather than slower interpreted code.

Ischemic stroke modeling requires multiscale coupling of electrophysiology with complex intracellular molecular alterations, and consideration of network properties in the context of bulk tissue alterations mediated by extracellular diffusion. Occlusion of a blood vessel in the brain triggers a cascade of changes, including: 1. synaptic glutamate release, related to excitotoxicity; 2. elevated extracellular potassium, leading to spreading depression; 3. cell swelling, reducing the extracellular volume and increasing the tortuosity; 4. production of reactive oxygen species, which give rise to inflammation. These cascades occur over multiple time-scales, with the initial rapid changes in cell metabolism and ionic concentrations triggering several damaging agents that may ultimately lead to cell death.

Acknowledgments: Research supported by NIH grant 5R01MH086638